

Published in final edited form as:

Am J Psychiatry. 2013 October 1; 170(10): 1134–1142. doi:10.1176/appi.ajp.2013.13030392.

Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial

James W. Murrough, M.D., Dan V. Iosifescu, M.D., Lee C. Chang, M.D., Rayan K. Al Jurdi, M.D., Charles M. Green, Ph.D., Andrew M. Perez, M.D., Syed Iqbal, M.D., Sarah Pillemer, B.A., Alexandra Foulkes, M.S., Asim Shah, M.D., Dennis S. Charney, M.D., and Sanjay J. Mathew, M.D.

Department of Psychiatry, the Department of Neuroscience, the Department of Anesthesiology, the Department of Pharmacology and Systems Therapeutics, and the Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York; the Department of Anesthesiology and the Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston; the Michael E. DeBakey VA Medical Center, Houston; and the Center for Clinical Research and Evidence-Based Medicine, University of Texas Medical School at Houston.

Abstract

Objective—Ketamine, a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist, has shown rapid antidepressant effects, but small study groups and inadequate control conditions in prior studies have precluded a definitive conclusion. The authors evaluated the rapid antidepressant efficacy of ketamine in a large group of patients with treatment-resistant major depression.

Method—This was a two-site, parallel-arm, randomized controlled trial of a single infusion of ketamine compared to an active placebo control condition, the anesthetic midazolam. Patients with treatment-resistant major depression experiencing a major depressive episode were randomly assigned under double-blind conditions to receive a single intravenous infusion of ketamine or midazolam in a 2:1 ratio (N=73). The primary outcome was change in depression severity 24 hours after drug administration, as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS).

Results—The ketamine group had greater improvement in the MADRS score than the midazolam group 24 hours after treatment. After adjustment for baseline scores and site, the MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% confidence interval [CI], 3.20 to 12.71). The likelihood of response at 24 hours was greater with ketamine than with midazolam (odds ratio, 2.18; 95% CI, 1.21 to 4.14), with response rates of 64% and 28%, respectively.

Address correspondence to Dr. Mathew (sjmathew@bcm.edu).
Drs. Murrough and Iosifescu contributed equally to this article.

Presented at the 51st annual meeting of the American College of Neuropsychopharmacology, Hollywood, Fla., Dec. 8–12, 2012; the 2013 annual meeting of the Anxiety and Depression Association of America, La Jolla, Calif., April 4–7, 2013; the 68th Annual Scientific Convention of the Society of Biological Psychiatry, May 16–18, 2013; and the 166th annual meeting of the American Psychiatric Association, San Francisco, May 18–22, 2013.

The other authors report no financial relationships with commercial interests.

Conclusions—Ketamine demonstrated rapid antidepressant effects in an optimized study design, further supporting NMDA receptor modulation as a novel mechanism for accelerated improvement in severe and chronic forms of depression. More information on response durability and safety is required before implementation in clinical practice.

Major depressive disorder is among the most disabling illnesses worldwide (1). A substantial proportion of patients do not achieve a clinically meaningful benefit despite multiple antidepressant trials and augmentation strategies (2, 3). Treatment-resistant major depression, defined as an insufficient response to at least two adequate antidepressant treatments, is associated with low rates of improvement with currently available antidepressant treatments (3, 4), and an intervention for refractory cases is thus an important unmet clinical need. Treatments that exert rapid antidepressant effects are a complementary unmet need, as the usual lag time to therapeutic effect is 4–12 weeks if patients show a response (2). Modulation of monoamine neurotransmitter systems (e.g., norepinephrine, dopamine, or serotonin) is the pharmacological mechanism underlying almost all current antidepressant agents, likely accounting for their similar efficacy and therapeutic time course (5). Therefore, engaging novel molecular targets outside of the monoamine system will likely be required in order to engender a clinically meaningful advance in depression therapeutics (6, 7).

Converging evidence from in vivo brain imaging studies, postmortem investigations, and gene expression studies implicates abnormalities in glutamatergic signaling in the pathophysiology of major depressive disorder (8–10). Ketamine—a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist—was associated with rapid antidepressant effects in patients with major depressive disorder (including treatment-resistant major depression) in several small studies and case reports (11–15). Antidepressant activity was observed within hours of a single subanesthetic intravenous infusion, representing a potential paradigm shift in therapeutic approaches for major depressive disorder. Methodological limitations of prior studies, however, including small study groups and the use of a crossover design with an inert placebo control condition (11, 12), precluded definitive conclusions regarding ketamine’s antidepressant efficacy. Identifying an appropriate control condition for testing the rapid antidepressant effects of ketamine has been particularly challenging since transient psychoactive effects associated with ketamine have the potential to undermine the integrity of the study blind.

We designed the present study to test the rapid antidepressant efficacy of ketamine in a relatively large group of subjects with treatment-resistant major depression, using an active placebo control condition (i.e., the anesthetic benzodiazepine midazolam) to optimize blinding and mitigate the influence of nonspecific factors on antidepressant outcome. We hypothesized that ketamine would be superior to midazolam in improving depressive symptoms 24 hours following a single infusion. The primary outcome at 24 hours was chosen to reflect a potential rapid antidepressant effect while avoiding any overlap with the expected transient psychoactive effects of ketamine or midazolam.

Method

Study Design and Patients

The study enrolled patients at two academic sites, Baylor College of Medicine and Icahn School of Medicine at Mount Sinai, between November 2010 and August 2012. Patients were eligible to participate if they were 21 to 80 years of age, had a primary diagnosis of major depressive disorder as assessed with the Structured Clinical Interview for DSM-IV—Patient Edition (16), and had an inadequate response to at least three therapeutic trials of an antidepressant according to the criteria of the Antidepressant Treatment History Form (17). The form was completed by a study psychiatrist using all available information from the patient report, information provided by a family member or caretaker, pharmacy records, and medical records. Additional study inclusion criteria included a history of at least one previous major depressive episode prior to the current episode (recurrent major depressive disorder) or the combination of a chronic major depressive episode (at least 2 years' duration) and a score of 32 or greater on the Inventory of Depressive Symptomatology—Clinician Rated (18) at screening and within 24 hours of infusion. Patients were excluded if they had a lifetime history of a psychotic illness or bipolar disorder, alcohol or substance abuse in the previous 2 years, unstable medical illness, serious and imminent suicidal or homicidal risk, or a score less than 27 on the Mini-Mental State Examination (19) or if they were taking contraindicated medications. Each patient had a physical examination, routine hematologic and biochemical tests, urine toxicology measurements, and an electrocardiogram (ECG) to detect unstable medical illness or substance use.

The institutional review boards at both participating sites approved the study. After complete description of the study to the subjects, written informed consent was obtained.

Study Procedures

The study patients were free of concomitant antidepressants and other psychotropic medications for the duration of the study with the exception of a stable dose of a nonbenzodiazepine hypnotic (e.g., zolpidem, 10 mg nightly). The protocol required patients to be drug free prior to the infusion, for at least 4 weeks for patients who were taking fluoxetine and for at least 1 week for those taking other medications.

Randomly assigned in a 2:1 ratio, the patients received a single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) or midazolam (0.045 mg/kg) infused over 40 minutes. Selection of midazolam—a short-acting benzodiazepine and anesthetic agent—as the control condition was based in part on pharmacokinetic characteristics similar to those of ketamine: fast onset of action and short elimination half-life (20). We sought to provide an anesthetic agent as a control condition that would mimic ketamine in terms of the time course of nonspecific behavioral effects (e.g., sedation, disorientation). The selected midazolam dose of 0.045 mg/kg is considered equipotent to 0.5 mg/kg of ketamine (21). The study research pharmacist prepared sealed envelopes that contained the drug identity; all other study personnel, including investigators, anesthesiologists, raters, patients, and data analysts, were masked to treatment assignment.

Following admission to a clinical research unit and an overnight fast, an indwelling catheter was placed in the antecubital vein of the nondominant arm, and pulse, blood pressure, digital pulse oximetry, and ECG monitoring were instituted, according to procedures previously described (13, 22). A trained rater conducted symptom ratings during the infusion and for 240 minutes following the start of the infusion. Patients were discharged from the research unit 24 hours after the infusion and received outpatient evaluations 48 hours, 72 hours, and 7 days postinfusion. The patients were instructed to abstain from psychotropic medications and to abstain from substances of abuse and alcohol while at home. Nonresponders were considered patients with less than 50% improvement from baseline in the score on the Montgomery-Åsberg Depression Rating Scale (MADRS) (23). As directed by the protocol, we stopped following the nonresponders 7 days after the infusion. Responders were followed biweekly until relapse or for an additional 4 weeks, whichever came sooner.

Outcomes

The primary outcome was reduction in depression severity as assessed on the clinician-administered MADRS (23) 24 hours following infusion. Trained raters, who were not involved in the infusion-day procedures and who were unaware of treatment-group assignment and infusion-related side effects, performed clinical assessments for the primary outcome at 24 hours and subsequent evaluations. The raters were experienced research staff extensively trained in the use of the instruments, and the MADRS rating conventions were pilot tested in prior ketamine studies in treatment-resistant major depression (13, 22). The two primary raters at each site achieved a high level of interrater reliability, 0.988.

Prior studies suggest that the peak antidepressant effects of ketamine occur within 24 hours of administration (12, 13). We selected the 24-hour change in depression severity as the primary endpoint for the current study because the interval after infusion was considered long enough that acute sedating and other side effects were not likely to be contributory. The interval was sufficiently short such that the individuals who showed substantial mood improvement were unlikely to have already relapsed. Secondary outcomes included the MADRS response rate (defined as a reduction in the baseline score by 50% or more), change in score on the Quick Inventory of Depressive Symptomatology—Self-Report (24), scores on the Clinical Global Impression (CGI) severity and improvement measures (25), and durability of benefit for up to 7 days following infusion.

We recorded general adverse events, dissociative states, and psychotomimetic side effects at regular intervals throughout the study, using the Patient Rated Inventory of Side Effects (26), the Clinician-Administered Dissociative States Scale (27), and the Brief Psychiatric Rating Scale positive symptom subscale (28), respectively.

Statistical Analysis

Power estimates for continuous MADRS scores and dichotomous response outcomes each assumed a two-tailed alpha level of 0.05. Conservative effect size estimates, Cohen's $d=0.71$ for MADRS scores and response rates of 60% versus 15% for ketamine and midazolam, respectively, were derived from previous reports (11, 12). A planned study group of 72 patients randomly assigned in a 2:1 ratio (ketamine versus midazolam) provided 80% and

96% power to detect a change in MADRS scores and response rates, respectively, at 24 hours as a function of treatment.

Modified intention-to-treat analyses included all randomly assigned patients with baseline measurement and at least one postbaseline measurement. Sensitivity analyses evaluated the robustness of conclusions in relation to missing data. We used general linear modeling (with the Proc Mixed function of SAS version 9.3 [SAS Institute, Cary, N.C.]) to examine MADRS scores at 24 hours as a function of treatment after controlling for baseline MADRS score and site. Exact logistic regression (Proc Logistic function, SAS version 9.3) evaluated response as a function of treatment group after adjustment for site.

Secondary analyses of scores on the Quick Inventory of Depressive Symptomatology and CGI severity and improvement scales employed general linear modeling and ordinal logistic regression (Proc Logistic, SAS), respectively, to evaluate treatment after adjustment for baseline measurements and site. Among the responders, general linear mixed modeling was used to evaluate the trajectory of change in the follow-up MADRS scores as a function of time, treatment, and the interaction of time and treatment. All statistical tests used a threshold of $p < 0.05$ for significance. Safety and tolerability were analyzed with the use of descriptive statistics.

Results

Study Participants

Of 116 patients who completed informed consent procedures, 73 met all eligibility criteria and were randomly assigned to the study medications. Of these 73, all but one patient (assigned to the ketamine group) received a study medication and completed 24-hour assessments (as shown in Figure SF1 in the data supplement accompanying the online version of this article). Sixty-seven patients completed all assessments through postinfusion day 7.

The ketamine and midazolam groups were wellmatched with respect to demographic and clinical characteristics. The patients were chronically depressed, had had relatively early illness onsets, and had moderate-to-severe symptom severity (Table 1).

Primary Outcome

Patients in the ketamine group had significantly greater improvement in the MADRS score at 24 hours than the midazolam group (Table 2). After adjustment for baseline scores and site, the mean MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% confidence interval [CI], 3.20 to 12.71), corresponding to a Cohen's d of 0.81. MADRS scores at 24 hours did not differ as a function of site ($F=0.63$, $df=1, 70$, $p=0.43$).

Secondary Outcomes

Additional 24-hour outcomes—Consistent with the primary outcome, the likelihood of treatment response at 24 hours was greater for the ketamine group than for the midazolam group (odds ratio, 2.18; 95% CI, 1.21 to 4.14; $p < 0.006$); the response rates were 64% and

28%, respectively. This represents a **number needed to treat of 2.8**. After adjustment for baseline scores and site, the mean score on the Quick Inventory of Depressive Symptomatology—Self-Report was lower in the ketamine group than in the midazolam group by 3.40 points (95% CI, 0.78 to 6.01; $p = 0.02$), corresponding to a Cohen's d of 0.63 (Table 2). Responder status at 24 hours did not differ as a function of site (exact $p=0.19$). Ketamine also improved the odds of being rated as improved or much improved on the CGI improvement measure (odds ratio, 2.31; 95% CI, 1.25 to 4.66; $p = 0.004$) and the odds of being rated as minimally or not at all ill on the CGI severity measure (odds ratio, 4.08; 95% CI, 1.76 to 13.51, $p = 0.001$) (Table 2).

Durability of drug effect—General linear mixed modeling was used to evaluate MADRS scores at 1, 2, 3, and 7 days after infusion as a function of treatment, time, and the interaction of treatment and time, after adjustment for site. While the analyses demonstrated main effects for time ($F=7.62$, $df=1$, 202, $p = 0.006$) and treatment ($F=5.93$, $df=1$, 202, $p = 0.02$), they failed to identify differential change over time as a function of treatment ($F=0.31$, $df=1$, 202, $p = 0.58$). When the analysis controlled for treatment, both groups demonstrated a small worsening in MADRS scores for every additional day postinfusion ($b=0.0004$; 95% CI, 0.00009 to 0.00062). When the scores were collapsed across time, patients in the ketamine group had lower MADRS scores (mean, 16.93; 95% CI, 14.03 to 19.82) than patients in the midazolam group (mean, 23.19; 95% CI, 19.03 to 27.34 ($t=2.44$, $df=202$, $p = 0.02$; Figure 1). The MADRS scores at day 7 did not differ as a function of site ($F=1.81$, $df=1$, 66, $p=0.18$).

Similarly, when the probability of treatment response was modeled as a function of time, treatment group, and the interaction of treatment and time, there was a main effect of time ($F=8.04$, $df=1$, 202, $p = 0.006$) and a main effect of treatment ($F=6.61$, $df=1$, 202, $p = 0.02$), but we failed to identify differential trajectories of change over time as a function of treatment ($F=0.12$, $df=1$, 202, $p = 0.73$). The effects of time and treatment corresponded to an increase in the probability of being a nonresponder over time and an increase in the probability of being a responder as a function of assignment to ketamine (Figure 2).

When the analysis adjusted for site and baseline scores, the scores on the MADRS and Quick Inventory of Depressive Symptomatology—Self-Report at 7 days post-infusion no longer demonstrated a statistically significant difference between treatment groups. Responder status at day 7 did not differ as a function of site (exact $p=0.11$). Similarly, there was no significant difference between groups in the response rate or the proportion of patients with CGI improvement scores of 2 or less. Relative to midazolam, ketamine demonstrated greater odds of a CGI severity score of 2 or less after 7 days (odds ratio, 2.26; 95% CI, 1.07 to 5.76) (see Table ST1 in the online data supplement).

At day 7, four patients in the midazolam group and 21 in the ketamine group still met the criteria for response and elected to continue in the study. For these 7-day responders, Figure 3 displays the time to relapse over the subsequent 4 weeks.

Adverse Events

The most common adverse events in the ketamine group for up to 4 hours after infusion were dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration, and restlessness. Within this same time period, the most common adverse events in the midazolam group were general malaise, dizziness, headache, restlessness, nausea or vomiting, dry mouth, decreased energy, and poor coordination (Table 3).

Eight of the 47 patients receiving ketamine (17%) had significant dissociative symptoms (i.e., feeling outside of one's body or perceiving that time is moving more slowly or more quickly than normal) immediately after the ketamine infusion; these symptoms resolved by 2 hours postinfusion. No severe psychotic symptoms (paranoia, hallucinations, delusions, or thought disorder) occurred in any patient (see Table ST2 and Figure SF2 in the online data supplement).

On average, mild transient changes in blood pressure were observed on the infusion day (Table 4). The infusion was discontinued for two patients in the ketamine group because of hemodynamic changes. In one case, a blood pressure elevation (peak, 187/91 mm Hg) unresponsive to beta-blocker therapy resulted in infusion termination after 30 minutes. The blood pressure normalized within 10 minutes of infusion cessation. In the other case, there was transient but pronounced hypotension and bradycardia that resolved without sequelae and was followed by overnight observation in the hospital (see Table ST3 in the online data supplement for a description of the serious adverse events).

Discussion

In this two-site trial in treatment-resistant patients with moderate-to-severe and persistent depressive symptoms, we found that a single low dose of ketamine, as compared with a psychoactive placebo control medication, was associated with a rapid-onset antidepressant effect. We found marked improvements in clinician-administered and patient self-report ratings of depression severity 24 hours after the ketamine infusion. The ketamine responders generally maintained the gains for several days beyond the 24-hour time point; we no longer observed statistically significant differences between treatment groups 7 days following the infusion. These data provide new support for the hypothesis that NMDA receptor modulation can accelerate clinical improvement in patients with severe and chronic forms of depression.

We consistently demonstrated the magnitude and duration of ketamine's benefit across two sites in an ethnically and racially diverse patient group, enhancing confidence in the reliability of these findings. The large and rapid antidepressant effect of ketamine we observed in these patients with a history of three or more failed antidepressant trials is especially significant given the poor prognosis for improvement with currently available antidepressant treatments in treatment-resistant major depression (3–5, 29). To maximize internal and external validity, we standardized infusion-monitoring procedures and shielded the primary outcome rater from knowledge of side effects on the day of infusion.

Improvements in secondary outcomes of global illness severity also supported the efficacy of ketamine in this trial.

Patients in the ketamine group experienced transient psychoactive and hemodynamic effects consistent with those in previous reports and clinical experience (11–15). Ketamine treatment did not increase the risk of emergent psychotic or manic symptoms over the follow-up period (see Figure SF2 in the data supplement accompanying the online version of this article). These findings suggest that ketamine is safe in the short term for nonpsychotic depressed patients when administered at a subanesthetic dose of 0.5 mg/kg over 40 minutes. It is important to note that the safety and efficacy of ketamine in depression beyond a single infusion are largely unknown and that abuse liability and other safety concerns associated with ketamine dictate a cautious approach to its application outside of research (30, 31). The observed hemodynamic changes in a subgroup of patients in our study encourage cardiorespiratory monitoring as an essential component of risk management.

The use of the anesthetic benzodiazepine midazolam as a control condition is a strength of the current study, although there is likely no perfect control condition for ketamine. Our objective was to select an agent that would function as a placebo (devoid of specific antidepressant effects) yet induce transient psychoactive effects designed to enhance study blinding and mitigate the nonspecific salutary impact of receiving an anesthetic agent. While the rates of general adverse events were similar across the two conditions, transient dissociative side effects immediately following study drug infusion were higher in the ketamine condition. Other agents that we considered for use as an active placebo included a sympathomimetic agent such as amphetamine. Amphetamine would have mimicked more closely the known sympathomimetic effects of ketamine (30); however, in contrast to midazolam, amphetamine is devoid of anesthetic properties. Finally, while we considered using a true active comparator with intrinsic antidepressant properties, we found that no pharmaceutical agents were readily available that had established antidepressant properties across a time scale similar to that for ketamine. Following the establishment of the antidepressant properties of ketamine in an optimized placebo-controlled design, future studies may compare schedules of ketamine to active comparators such as electroconvulsive therapy or antidepressant-antipsychotic medication combinations.

The biological mechanisms underlying ketamine's antidepressant activity remain largely unknown. The rapid onset of antidepressant activity we observed is consistent with preclinical work indicating that ketamine rapidly (within hours) increases the number and functioning of synaptic connections involving cortical or hippocampal neurons (32–34). Ketamine appears to rapidly reverse both behavioral and neuronal changes associated with chronic stress, in part through activation of the mammalian target of the rapamycin signaling pathway and stimulation of brain-derived neurotrophic factor signaling (35). It is interesting that a recent study of patients with major depressive disorder found that carriers of the Val66Met (rs6265) single nucleotide polymorphism—representing an attenuation of BDNF functioning—had a smaller antidepressant response to ketamine (36), in line with findings in animal models (34, 37, 38).

Limitations of our trial include stringent enrollment criteria due to concerns about ketamine's psychoactive effects and abuse liability. We believe that the exclusion of patients with histories of psychotic symptoms or substance or alcohol use disorders does not diminish the generalizability of our findings but, rather, offers a clinically relevant risk-mitigation strategy. A proportion of screened patients (17.2%) refused or were unable to tolerate psychotropic medication washout prior to randomization, thereby restricting participants to medication-free individuals or those able to tolerate medication washout. The efficacy of ketamine as an adjunct to ongoing therapies is a clinically relevant question not addressed in our study. Finally, we tested the efficacy of a single infusion over a brief follow-up period. The transient antidepressant response to ketamine highlights the need to identify strategies to maintain and prolong the initial response. Two studies of the glutamate-modulating drug riluzole failed to find benefit in prevention of relapse following ketamine administration (13, 39). Additional infusions of ketamine have recently been explored to prolong the antidepressant response (22, 40), although controlled data testing this strategy are not currently available.

In conclusion, treatment-resistant patients in a major depressive episode showed a rapid antidepressant response to a single infusion of ketamine. To our knowledge, the current study represents the largest investigation to date of ketamine in treatment-resistant major depression. Utilizing an optimized active placebo design, the trial provides new evidence for the specific antidepressant effects of ketamine, apart from its nonspecific anesthetic properties. Future research is required to test the antidepressant effects of ketamine beyond a single administration and to characterize its longer-term safety profile.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by NIMH grant RO1 MH-081870 to Dr. Mathew, by grant UL1 TR000067 from the NIH National Center for Advancing Translational Sciences, by the Department of Veterans Affairs (VA), by a NARSAD Independent Investigator Award and funding from the Brown Foundation, Inc., to Dr. Mathew, by resources and facilities at the Michael E. DeBakey VA Medical Center, and by NIMH Career Development Award 1K23 MH-094707 to Dr. Murrough.

The authors thank J. Moral, D. Reich, J. Joseph, S. Caress, R. de la Garza II, C. Levitch, J. Mahoney, T. Newton, P. Atluri, and M. Suresh.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

References

1. Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, Anderson W, Dhansay MA, Phillips A, Shurin S, Walport M, Ewart W, Savill SJ, Bordin IA, Costello EJ, Durkin M, Fairburn C, Glass RI, Hall W, Huang Y, Hyman SE, Jamison K, Kaaya S, Kapur S, Kleinman A, Ogunniyi A, Otero-Ojeda A, Poo MM, Ravindranath V, Sahakian BJ, Saxena S, Singer PA, Stein DJ. Scientific Advisory Board and the Executive Committee of the Grand Challenges on Global Mental Health: Grand challenges in global mental health. *Nature*. 2011; 475:27–30. [PubMed: 21734685]

2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006; 163:1905–1917. [PubMed: 17074942]
3. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, Shores-Wilson K, Niederehe G, Fava M. STAR*D Study Team: Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006; 354:1231–1242. [PubMed: 16554525]
4. Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, Ritz L, Nierenberg AA, Lebowitz BD, Biggs MM, Luther JF, Shores-Wilson K, Rush AJ. STAR*D Study Team: Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006; 354:1243–1252. [PubMed: 16554526]
5. Murrough JW, Charney DS. Is there anything really novel on the antidepressant horizon? *Curr Psychiatry Rep*. 2012; 14:643–649. [PubMed: 22996298]
6. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature*. 2008; 455:894–902. [PubMed: 18923511]
7. Li X, Frye MA, Shelton RC. Review of pharmacological treatment in mood disorders and future directions for drug development. *Neuropsychopharmacology*. 2012; 37:77–101. [PubMed: 21900884]
8. Manji HK, Quiroz JA, Sporn J, Payne JL, Denicoff K, Gray NA, Zarate CA Jr, Charney DS. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol Psychiatry*. 2003; 53:707–742. [PubMed: 12706957]
9. Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov*. 2008; 7:426–437. [PubMed: 18425072]
10. Skolnick P, Popik P, Trullas R. Glutamate-based antidepressants: 20 years on. *Trends Pharmacol Sci*. 2009; 30:563–569. [PubMed: 19837463]
11. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000; 47:351–354. [PubMed: 10686270]
12. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an Nmethyl- D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006; 63:856–864. [PubMed: 16894061]
13. Mathew SJ, Murrough JW, Aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. *Int J Neuropsychopharmacol*. 2010; 13:71–82. [PubMed: 19288975]
14. Aan Het Rot M, Zarate CA Jr, Charney DS, Mathew SJ. Ketamine for depression: where do we go from here? *Biol Psychiatry*. 2012; 72:537–547. [PubMed: 22705040]
15. Mathew SJ, Shah A, Lapidus K, Clark C, Jarun N, Ostermeyer B, Murrough JW. Ketamine for treatment-resistant unipolar depression: current evidence. *CNS Drugs*. 2012; 26:189–204. [PubMed: 22303887]
16. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), version 2. New York: New York State Psychiatric Institute, Biometrics Research; 1995.
17. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001; 62(suppl 16):10–17. [PubMed: 11480879]
18. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996; 26:477–486. [PubMed: 8733206]
19. Folstein MF, Folstein SE, McHugh PR. “Mini-Mental State”: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–198. [PubMed: 1202204]

20. Kanto JH. Midazolam: the first water-soluble benzodiazepine: pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. *Pharmacotherapy*. 1985; 5:138–155. [PubMed: 3161005]
21. Gross JB, Caldwell CB, Edwards MW. Induction dose-response curves for midazolam and ketamine in premedicated ASA class III and IV patients. *Anesth Analg*. 1985; 64:795–800. [PubMed: 3160264]
22. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, Aan Het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry*. (Epub ahead of print, July 26, 2012).
23. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; 134:382–389. [PubMed: 444788]
24. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003; 54:573–583. [PubMed: 12946886]
25. Guy, W., editor. *ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76–338*. Washington, DC: US Department of Health, Education, and Welfare; 1976. p. 218–222.
26. Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, Thase ME, Nierenberg AA, Quitkin FM, Kashner TM, Kupfer DJ, Rosenbaum JF, Alpert J, Stewart JW, McGrath PJ, Biggs MM, Shores-Wilson K, Lebowitz BD, Ritz L, Niederehe G. STAR*D Investigators Group: Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. *Control Clin Trials*. 2004; 25:119–142. [PubMed: 15061154]
27. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress*. 1998; 11:125–136. [PubMed: 9479681]
28. Overall JE, Gorham DR, Shawver JR. Basic dimensions of change in the symptomatology of chronic schizophrenics. *J Abnorm Soc Psychol*. 1961; 63:597–602. [PubMed: 14482841]
29. Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. *CNS Drugs*. 2010; 24:131–161. [PubMed: 20088620]
30. White JM, Ryan CF. Pharmacological properties of ketamine. *Drug Alcohol Rev*. 1996; 15:145–155. [PubMed: 16203365]
31. Morgan CJ, Muetzelfeldt L, Curran HV. Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. *Addiction*. 2009; 104:77–87. [PubMed: 19133891]
32. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010; 329:959–964. [PubMed: 20724638]
33. Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, Li XY, Aghajanian G, Duman RS. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry*. 2011; 69:754–761. [PubMed: 21292242]
34. Liu RJ, Lee FS, Li XY, Bambico F, Duman RS, Aghajanian GK. Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. *Biol Psychiatry*. 2012; 71:996–1005. [PubMed: 22036038]
35. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. 2012; 338:68–72. [PubMed: 23042884]
36. Laje G, Lally N, Mathews D, Brutsche N, Chemerinski A, Akula N, Kelmendi B, Simen A, McMahon FJ, Sanacora G, Zarate C Jr. Brain-derived neurotrophic factor Val66Met polymorphism and antidepressant efficacy of ketamine in depressed patients. *Biol Psychiatry*. 2012; 72:e27–e28. [PubMed: 22771240]
37. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011; 475:91–95. [PubMed: 21677641]

38. Kavalali ET, Monteggia LM. Synaptic mechanisms underlying rapid antidepressant action of ketamine. *Am J Psychiatry*. 2012; 169:1150–1156. [PubMed: 23534055]
39. Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, Moaddel R, Wainer I, Luckenbaugh DA, Manji HK, Zarate CA Jr. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology*. 2012; 37:1526–1533. [PubMed: 22298121]
40. van het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, Mathew SJ. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry*. 2010; 67:139–145. [PubMed: 19897179]

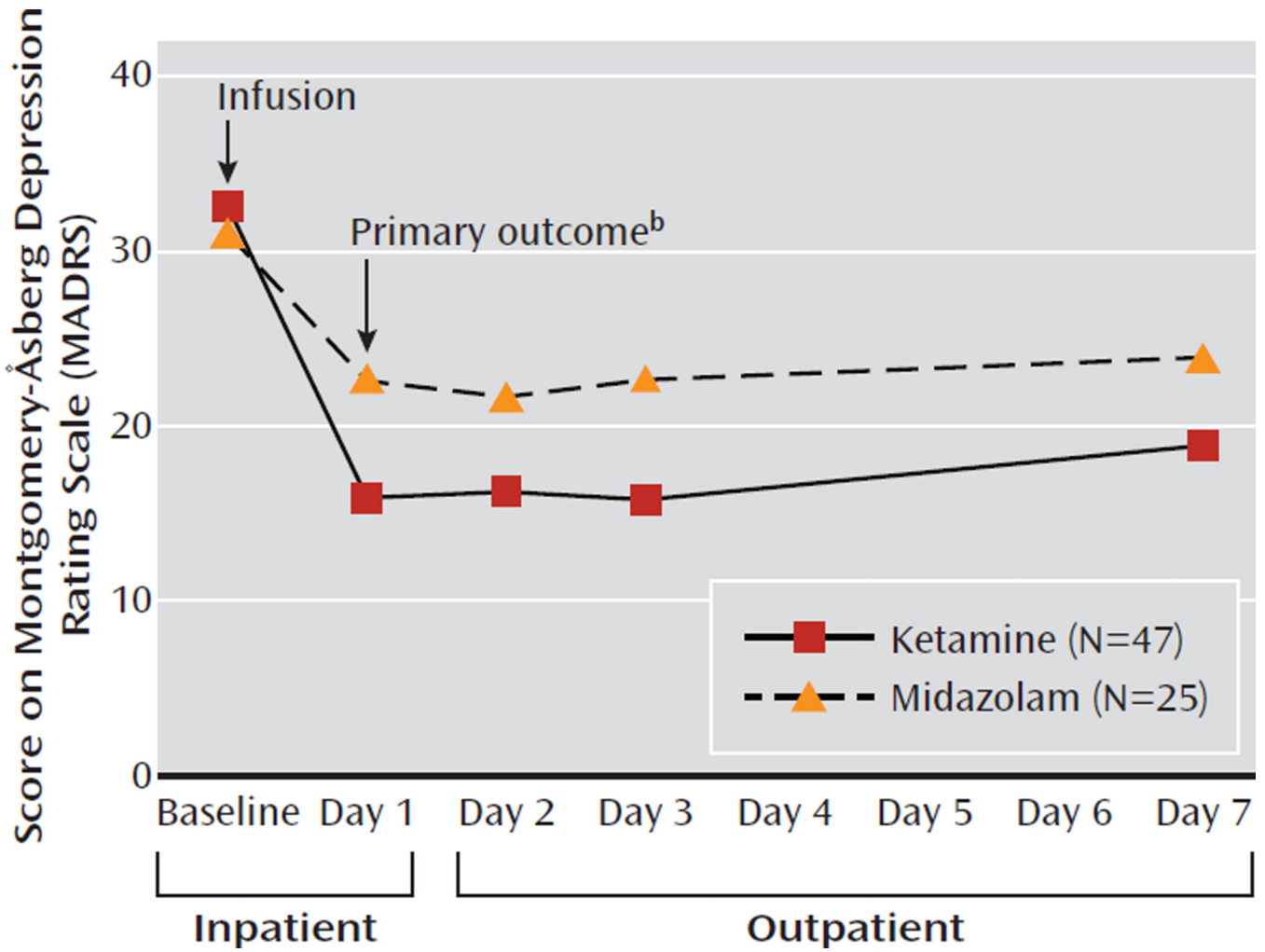


FIGURE 1.

Change in Depression Severity Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolama

^a Modified intention-to-treat group. MADRS scores range from 0 to 60, with higher scores indicating a greater severity of symptoms.

^b Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group (p = 0.002).

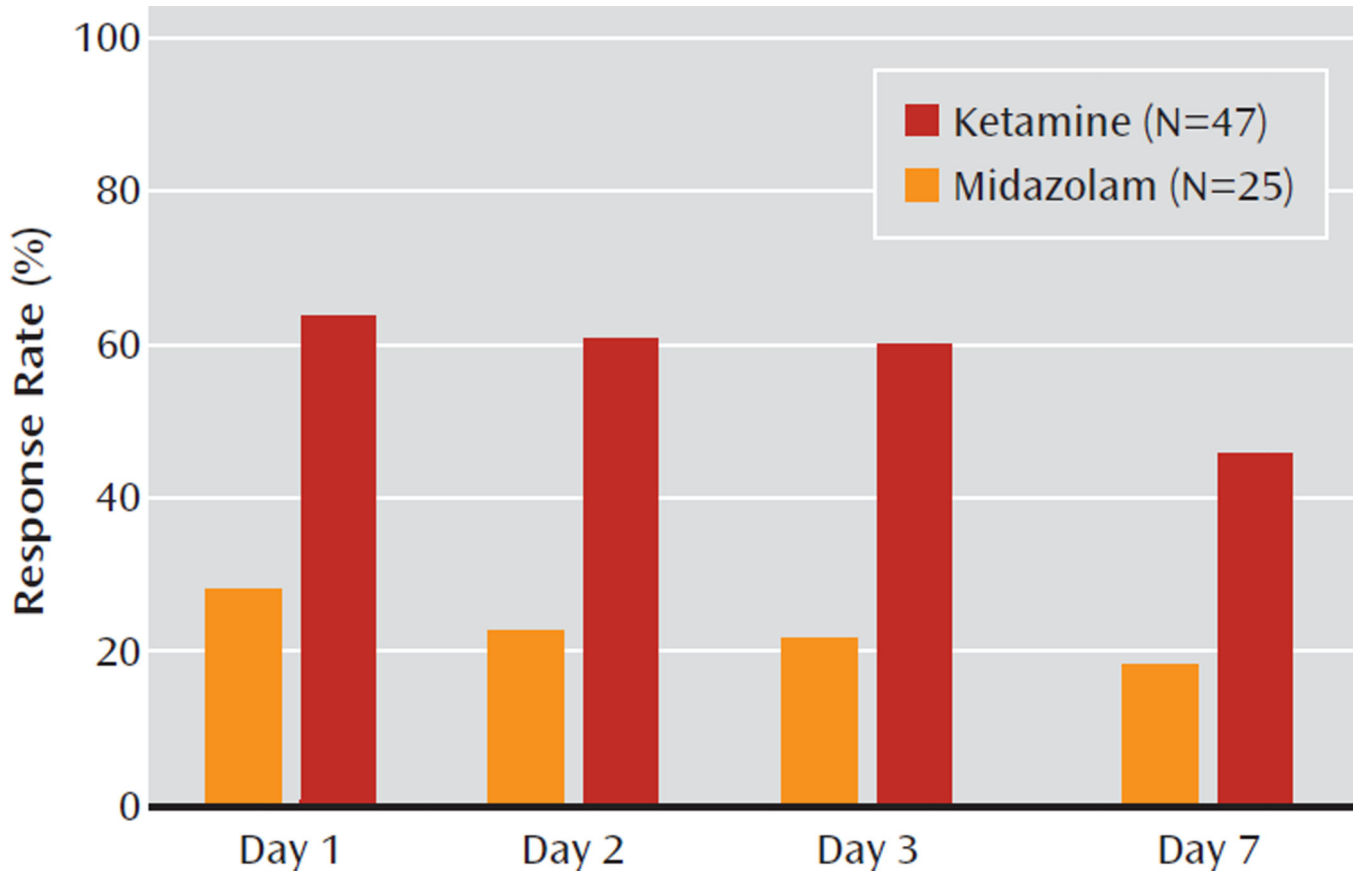


FIGURE 2.

Response Rates Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolama

^a Modified intention-to-treat group. Response at each time point was defined as a decrease from baseline of at least 50% in score on the Montgomery-Åsberg Depression Rating Scale.

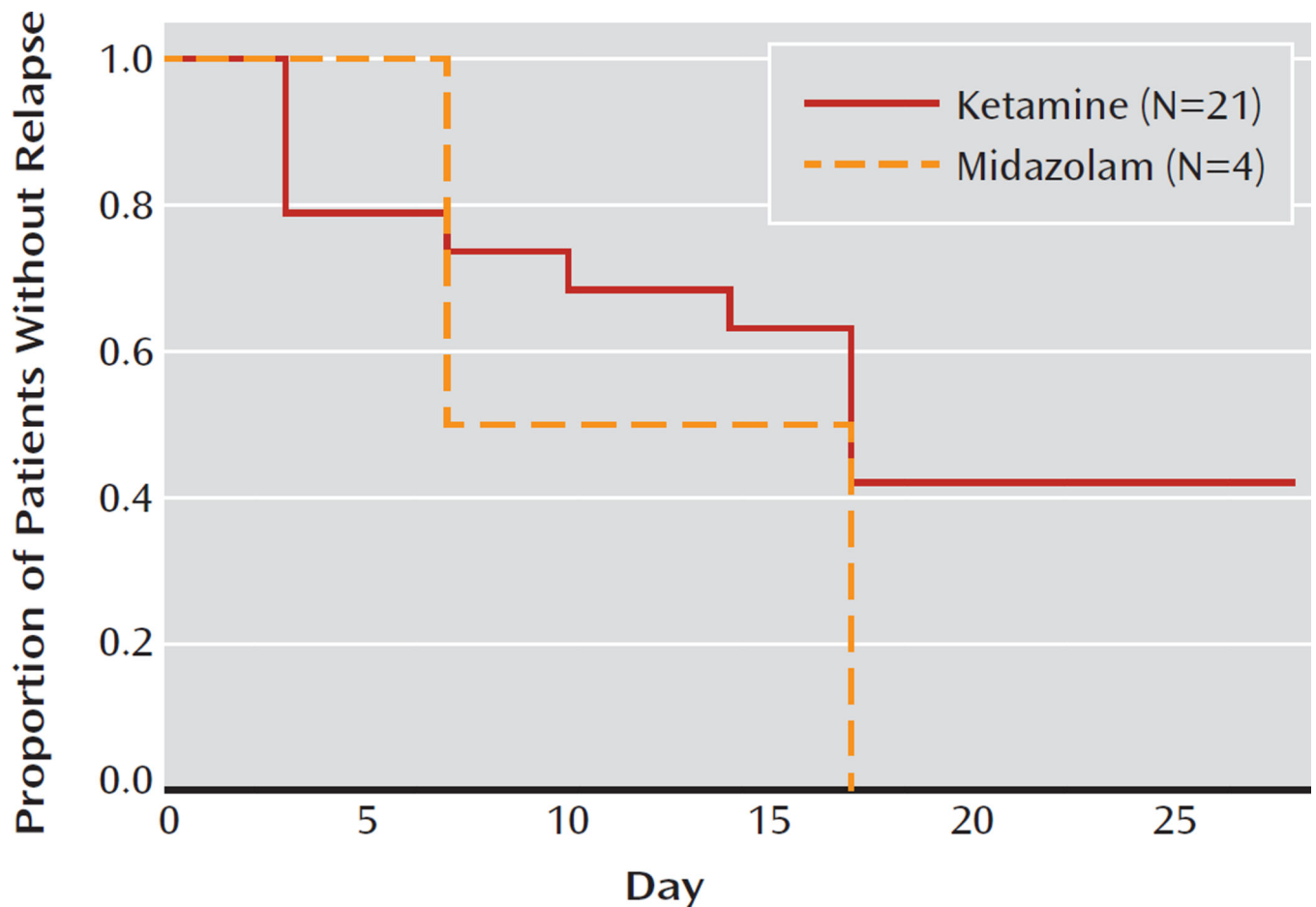


FIGURE 3.

Time to Relapse for Responders at Day 7 Among Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolama

^a Response was defined as a decrease from baseline of at least 50% in score on the Montgomery-Åsberg Depression Rating Scale (MADRS). Relapse was defined as a MADRS score of 20 or higher maintained for two consecutive visits and meeting criteria for a major depressive episode for 1 week.

TABLE 1

Characteristics of Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam^a

Characteristic	Ketamine (N=47)		Midazolam (N=25)	
	N	%	N	%
Female sex	26	55	11	44
White	37	79	23	92
Hispanic ethnicity	7	15	3	12
Recurrent major depressive disorder	28	60	16	64
Chronic index episode (lasting ≥ 2 years)	33	70	16	64
Prior suicide attempt	14	30	9	36
Prior psychiatric hospitalization	23	49	13	52
Melancholic features	31	66	16	64
Atypical features	4	9	6	24
Unemployed	27	57	15	60
Married or cohabiting	19	40	10	40
	Mean	SD	Mean	SD
Number of major depressive episodes	3.7	3.7	4.0	3.4
Duration of index episode (months)	146.6	158.3	109.2	139.0
Previous antidepressant failures	5.1	2.0	5.0	1.8
Age (years)	46.9	12.8	42.7	11.6
Education (years)	16.5	2.3	16.2	2.3
Age at first major depressive episode (years)	22.2	9.9	19.8	9.8
Duration of major depressive disorder (years)	24.2	12.5	19.7	14.8
Body mass index (kg/m ²)	29.4	7.5	27.0	6.1
Scores on clinical measures 30-item Inventory of Depressive Symptomatology—Clinician Rated ^b	48	9	48	10
Montgomery-Åsberg Depression Rating Scale ^c	32.6	6.1	31.1	5.6
16-item Quick Inventory of Depressive Symptomatology—Self-Report ^d	16.6	4.1	16.3	4.5

^aModified intention-to-treat group.

^bScores range from 0 to 84, with higher scores indicating a greater severity of symptoms.

^cScores range from 0 to 60, with higher scores indicating a greater severity of symptoms.

^dScores range from 0 to 27, with higher scores indicating a greater severity of symptoms.

TABLE 2

Clinical Status at 24 Hours of Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam^a

Clinical Measure	Ketamine (N=47)		Midazolam (N=25)	
	Mean	95% CI	Mean	95% CI
Montgomery-Åsberg Depression Rating Scale (MADRS) score ^b	14.77	11.73–17.80	22.72	18.85–26.59
Quick Inventory of Depressive Symptomatology—Self Report score ^c	8.38	6.71–10.05	11.78	9.63–13.92
	N	%	N	%
Response: 50% decrease in MADRS score ^d	30	64	7	28
Clinical Global Impression Scale				
Improvement rating of 2 (much improved) or 1 (very much improved) ^e	29	62	6	24
Severity rating of 2 (minimally ill) or 1 (not at all ill) ^f	25	53	2	8

^aModified intention-to-treat group.

^bSignificantly lower score in the ketamine group ($t=3.34$, $df=68$, $p=0.001$).

^cSignificantly lower score in the ketamine group ($t=6.69$, $df=68$, $p=0.01$).

^dSignificantly higher proportion in the ketamine group ($p=0.006$, exact logistic regression).

^eSignificantly higher proportion in the ketamine group ($p=0.004$, ordinal logistic regression).

^fSignificantly higher proportion in the ketamine group ($p=0.001$, ordinal logistic regression).

TABLE 3
 Adverse Events in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine (N=47) or Midazolam (N=25)

Adverse Event ^a	Infusion Day ^b						Days 1-7 After Infusion ^c									
	New Onset or Worsening			Distressing			New Onset or Worsening			Distressing						
	Ketamine	Midazolam	%	Ketamine	Midazolam	%	Ketamine	Midazolam	%	Ketamine	Midazolam	%				
Gastrointestinal																
Nausea/vomiting	16	34	3	12	3	6	1	4	7	15	2	8	1	2	0	0
Dry mouth	12	26	4	16	2	4	2	8	4	9	3	12	1	2	0	0
Constipation	2	4	0	0	0	0	0	0	4	9	1	4	1	2	0	0
Diarrhea	2	4	1	4	1	2	0	0	9	19	4	16	1	2	0	0
Heart																
Dizziness on standing	10	21	2	8	3	6	0	0	6	13	5	20	2	4	1	4
Palpitation	5	11	0	0	2	4	0	0	6	13	2	8	2	4	0	0
Chest pain	2	4	0	0	1	2	0	0	2	4	2	8	0	0	0	0
Skin																
Increased perspiration	5	11	1	4	1	2	1	4	5	11	1	4	0	0	0	0
Itching	2	4	1	4	2	4	0	0	6	13	1	4	1	2	0	0
Dry skin	1	2	1	4	1	2	1	4	12	26	5	20	1	2	0	0
Rash	1	2	0	0	1	2	0	0	5	11	1	4	1	2	0	0
Nervous system																
Dizziness	21	45	5	20	6	13	1	4	6	13	1	4	2	4	0	0
Headache	15	32	5	20	4	9	1	4	15	32	7	28	3	6	1	4
Poor coordination	12	26	3	12	2	4	3	12	2	4	1	4	0	0	1	4
Tremors	6	13	0	0	0	0	0	0	3	6	2	8	1	2	1	4
Eyes or ears																
Blurred vision	20	43	2	8	5	11	1	4	5	11	2	8	1	1	0	0
ringing in ears	2	4	1	4	0	0	0	0	1	2	1	4	2	2	0	0
Genital/urinary																
Frequent urination	0	0	0	0	0	0	0	0	4	9	0	0	0	0	0	0

Blood Pressure of Patients With Treatment-Resistant Major Depression Following a Single Infusion of Ketamine or Midazolam

TABLE 4

Time	Blood Pressure (mm Hg)							
	Ketamine (N=47)				Midazolam (N=25)			
	Systolic	Diastolic	Mean	SD	Systolic	Diastolic	Mean	SD
Baseline	121.7	71.7	80.8	11.3	120.8	72.4	80.8	9.6
40 minutes after infusion	140.7	80.8	111.8	12.7	111.8	67.9	111.8	9.9
240 minutes after infusion	125.4	70.6	89	8.9	113.9	71.6	113.9	7.7